UNITED STATES DISCTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

ARIAD PHARMACEUTICALS, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, and THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE	)	Civil Action No. 02 CV 11280 RWZ
Plaintiffs,	)	U.S. District Judge Rya W. Zobel
v.	)	
ELI LILLY AND COMPANY,	)	
Defendant.	)	

MEMORANDUM IN SUPPORT OF DEFENDANT ELI LILLY AND COMPANY'S SECOND MOTION FOR JUDGMENT AS A MATTER OF LAW

I. INTRODUCTION

Eli Lilly and Company ("Lilly") is entitled to Judgment as a Matter of Law ("JMOL") finding the '516 patent not infringed and invalid. The evidence presented by Lilly regarding invalidity of the '516 patent is so compelling that no reasonable jury could find for Plaintiffs regardless of any evidence that Plaintiffs presented on the issue. Plaintiffs have also failed in their burden to introduce any evidence sufficient to prove direct or indirect infringement. Finally, Plaintiffs have introduced no evidence of lowered NF-kB activity in even a single patient taking Lilly's Evista® and Xigris® products and therefore Plaintiffs have failed on their burden to prove damages. A court should render judgment as a matter of law when "there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." *Fed. Rule Civ. Proc.* 50(a).

Lilly also renews their Motions for Summary Judgment of Invalidity Under 35 U.S.C. §§ 101 and 112, First Paragraph and Invalidity Under 35 U.S.C. § 102 with the addition of the testimony provided below[1]. "[T]he standard for granting summary judgment 'mirrors' the standard for judgment as a matter of law, such that "the inquiry under each is the same.'" *Zimmerman v. Direct Fed. Credit Union*, 121 F. Supp. 2d 133, 134 (D.Mass. 2000).

II. THE '516 PATENT IS INVALID UNDER 35 U.S.C. § 101

Plaintiffs own witnesses have testified to facts supporting Lilly's earlier filed Motion for Summary Judgment of Invalidity under 35 U.S.C. § 101. One of the fundamental principles of the United States patent laws is that a natural phenomenon cannot be patented. While the discovery of such a natural phenomenon might have an extraordinary impact upon science, the natural phenomenon itself is a basic tool or rudimentary knowledge that cannot be excluded from others through the patent system. The Supreme Court and many other courts have repeatedly held over the past 100 or more years that patent claims cannot properly cover "laws of nature, physical phenomena, and abstract ideas" *Diamond v. Diehr*, 450 U.S. 175, 185, 101 S.Ct. 1048, 1056, 67 L.Ed.2d 155 (1981); *see also, e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 67, 93 S.Ct. 253, 34 L.Ed.2d 273 (1972) ("Phenomena of nature, though just discovered…are not patentable, as they are the basic tools of scientific and technological work.")

The prohibition against patenting of natural phenomena applies equally to each of the categories of statutory subject matter enumerated in Section 101, including processes.

[1] Lilly's Memoranda in Support of their Motions for Summary Judgment are found at docket entries 176 and 172.

> Though every set of steps, of whatever nature, may properly be labeled a "process," §101 ("Whoever invents") limits the patent to invented processes. Sets of steps conducted entirely by nature are not subject to patenting; they are not invented by man.

In re Sarkar, 588 F.2d 1330, 1333 (C.C.P.A. 1979).

The claims of the '516 patent encompass natural methods of reducing NF-κB activity that have been and are being performed by nature in mammalian cells, without intervention by man, which is directly prohibited by U.S.C. §101[2]. The claims of the '516 patent encompass the cell's own method for reducing its NF-κB activity (the "autoregulatory loop"), which falls squarely within the realm of unpatentable subject matter outside the scope of 35 U.S.C. §101.

A. THE ASSERTED CLAIMS OF THE '516 PATENT ENCOMPASS THE NATURAL AUTOREGULATORY MECHANISM/FEEDBACK LOOP

Each of the limitations of the asserted claims of the '516 patent encompass the natural autoregulatory process and are thus invalid under 35 U.S.C. § 101. The autoregulatory or negative feedback loop refers to a natural process that occurs in cells whereby an induced increase in NF-κB activity necessarily results in an increase in the expression of the NF-κB inhibitor protein, IκB, which, in turn, intervenes in the NF-κB pathway and reduces NF-κB activity. Testimony by Plaintiff's witnesses have confirmed that the autoregulatory loop reduces NF-κB activity in cells and that such a process has occurred in nature for millions of years.

[2] Under the Court's claim construction order, the claims encompass any and all methods of "decreasing the function of NF-κB to act as an intracellular messenger that regulates transcription of particular genes, in response to certain stimuli." *Court's Claim Construction Order*.

Specifically, testimony by Dr. Sharp, one of the named inventors on the ‘516 patent, confirms that NF-κB and IκB are natural proteins performing natural activities that have occurred in cells for at least 30 million years.

Q.	And so, NF-kappaB existed in cells in nature before your work started?
A.	Well, we didn't know about NF-kappaB's existence until this work because it was coined in this work. So, the process existed, but it's being known as NF-kappaB came with this work.
Q.	Do you have any reason to believe that NF-kappaB didn't exist in cells for millions of years?
A.	No, I have no reason to believe it, but it wasn't known as NF-kappaB.
Q.	But, in fact, you do know that NF-kappaB did exist in cells for at least thirty million years; isn't that correct?
A.	Well, we know that there are NF-kappaB activities in cells in different organisms that probably were separated over that time period.
Q.	And so, NF-kappaB activity existed for at least thirty million years?
A.	Probably. NF-kappaB-type activity.
Q.	I won't quibble over five or ten million years, Dr. Sharp.
A.	Okay, thank you.
Q.	But for a very long time?
A.	For a very long time.
Q.	And because NF-kappaB activity has existed for a very long time, NF-kappaB itself has existed for a very long time, am I right?
A.	The activity we identified as NF-kappaB in this study probably has existed for a very long time.
Q.	And NF-kappaB is a protein, if I recall?
A.	Yes, it is.
Q.	And that protein has existed for a very long time?
A.	The protein itself has existed for a very long time.
Q.	So, you and your fellow inventors did not create the protein, NF-kappaB?
A.	Well, we created the knowledge that NF-kappaB exists in this patent.
Q.	But you didn't create the protein itself. It existed in nature?
A.	It existed without that name.

Trial Transcript, Day 3, 18:7-19:21

Q. And so, I-kappaB activity was part of cells in nature for a very long time?
A. Yes, without the name. Without the identification and without knowing about it.
Q. But it existed?
A. Yes, probably.
Q. Probably?
A. I wasn't around.
Q. Do you really think that I-kappaB activity came into existence only in the 1980s, Dr. Sharp?
A. Well, I can say in my laboratory we found it in 1980. And I can say in our laboratory we saw indications that it had been around as an activity before that by looking at different genes, but I didn't do experiments before 1980.
Q. I understand. And when you say before 1980, in fact it would be millions of years ago?
A. Probably, as we understand.

Trial Transcript, Day 3, 20:24-21:18.

Further, Dr. Maniatis, another named inventor of the '516 patent, provided direct testimony that the autoregulatory loop, which occurs naturally, reduces NF-κB activity in cells:

Q. When NF-kappaB is activated, one of the genes which is turned on is its natural inhibitor, I-kappaB, isn't it?
A. Yes.
Q. That in turn feeds backs to reduce NF-kappaB activity; isn't that correct?
A. It depends on the circumstances. It will feed back under certain circumstances, but, for example, if you have a cascade of activity, the on switch can be much stronger than the off switch and therefore can keep the gene going.
...

Q. But nevertheless, when a virus hits a cell and NF-kappaB turns on the expression of genes, one of those genes that it turns on is the gene that encodes I-kappaB; isn't that correct?
A. That's correct.
Q. And one of the proteins, here you show interferon, but another protein that naturally produced within the cell with activation of NF-kappaB is the gene for the protein that encodes the natural inhibitor; isn't that correct?
A. That is correct.

…

THE COURT: So what happens is that the virus comes and it activates the NF-kappaB by dissociating from the I-kappaB, right?
THE WITNESS: Right.
THE COURT: Then the NF-kappaB attaches to the gene, and that produces not only in this case interferon or the antibodies, but also produces the mechanism with which more I-kappaB can be produced?
THE WITNESS: That's correct.
Q. The additional I-kappaB that is produced will bind to NF-kappaB and prevent it from moving to the nucleus; isn't that correct?
A. Yes, but, again, you have to, you have to say that that's specific to the conditions, because if you're in a state, for example, sepsis, that doesn't happen, because you can't produce enough I-kappaB to shut down the system. It gets -- you know, the receptors on the cell surface are firing so fast that as the I-kappaB is made, it gets knocked out. So it's -- there's not an easy answer to this question, it is a feedback mechanism, but the efficacy of that feedback mechanism depends on the disease state.
Q. Well, the feedback mechanism occurred --

Trial Transcript, Day 3, 87:17-25; 88:20-89:4; 89:17-90:13.

Dr. Maniatis further provided a specific example of the NF-κB autoregulatory process, testifying that natural sunlight induces NF-κB activity, which, in turn, induces IκB gene expression, which is then in turn reduced by IκB through the natural autoregulatory loop mechanism:

Q.	Let's go back to the sunburn example, Dr. Manlaitis. If the inducer, instead of viruses as shown up here, is sunlight, sunlight hits the cell, activates NF-kappaB, and NF-kappaB comes down here to the gene that codes certain proteins and binds to an NF-kappaB recognition site there; is that correct?
A.	Uh-huh, uh-huh. Yes.
Q.	And turns on the gene for various proteins, and one of the genes that it turns on is the gene that encodes I-kappaB; isn't that correct?
A.	Yes.
Q.	So when sunlight hits the cell, you will see this feedback mechanism or auto-regulatory loop; isn't that correct?
A.	The problem is if you stay in the sun, it keeps going, so new I-kappaB is degraded as fast as it can be made.
Q.	Sure. If you put an umbrella over your head or step out of the sun, the auto-regulatory loop will kick in and reduce NF-kappaB activity within the cell; isn't that correct?
A.	Yes.
Q.	And this same process has been occurring since caveman times, at least, isn't that correct?
A.	Well, I would say that -- well, yes.

Trial Transcript, Day 3, 91:5-92:1.

Additionally, Dr. Maniatis further testified that the autoregulatory loop which reduces NF-kappaB activity in the cells would also reduce the expression of genes that are activated by NF-κB:

Q. Both of those will reduce NF-kappaB activity in the cells; isn't that correct, Dr. Manlaitis?
A. Both of what?
Q. The umbrella example and the auto-regulatory feedback mechanism with I-kappaB being produced by NF-kappaB?
A. Yes.
Q. So both of those will reduce NF-kappaB activity in the cells. And will they reduce expression of genes that are activated by sunlight in this particular case?
MS. BEN-AMI: This is a characterization of the claim.
THE COURT: I understand the witness to say that there are extracellular influences which do certain things, and you're skipping over the extracellular influences in your question.
MR. DRUTCHAS: No, your Honor. Let me come back to that.
THE COURT: The sun is the extracellular influence, isn't it?
THE WITNESS: That's right.
THE COURT: Reducing the sun is reducing the extracellular influence, and then that has the consequences in the patent. But that's not what you were asking about, as I understood it.
MR. DRUTCHAS: That's exactly what I'm asking about. Reducing the extracellular influence will reduce the NF-kappaB activity in the cells and reduce the expression of genes that are regulated by NF-kappaB; isn't that correct, Dr. Manlaitis?
A. It will reduce the expression of the genes that are induced by sunlight.
Q. And it will reduce the NF-kappaB activity in the cells as well; isn't that correct?
A. Yes.

Trial Transcript, Day 3, 93:23-95:7.

Q. Now, the auto-regulatory loop will also -- first of all, the auto-regulatory loop has no effect on the external influences, isn't that correct, this feedback mechanism?
A. It influences -- you mean does it affect the sunlight?
Q. Correct.
A. No.
Q. It just affects the cell's reaction to the sunlight, correct?
A. Yes.
Q. So the auto-regulatory loop will reduce NF-kappaB activity in the cells; isn't that correct?
A. Well, in the absence of the inducer, so in the absence of a virus or in the absence of bacteria, the steady state resting state of the cell will be reestablished.
Q. And it will also reduce the expression of genes that are regulated by NF-kappaB; isn't that correct?
A. Yes.

Trial Transcript, Day 3, 95:8-24.

Testimony by the named inventors, Dr. Sharp and Dr. Maniatis, confirmed that NF-κB activity is reduced in cells naturally through the autoregulatory loop and further confirmed that the reduction in NF-κB activity would also reduce the expression of genes that are activated by NF-κB. Thus, the claims of the '516 patent encompass natural processes that have been and are being performed by nature in cells, without intervention by man, which is directly prohibited by U.S.C. §101.

III. THE '516 PATENT IS INVALID UNDER 35 U.S.C. § 102

Lilly contends that the '516 patent is invalid under 35 U.S.C. § 102(b) because "the invention [reduction of NF-κB activity] was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." A single prior art reference anticipates a patent claim if it expressly or inherently describes each and every limitation set forth in the patent claim. *Trintec lnd., lnc. v. Top-U.S.A. Corp*, 295 F.3d 1292, 1295 (Fed.Cir. 2002) (citing *Verdegaal Bros., Inc. v. Union Oil Co.,* 814 F.2d 628, 631 (Fed.Cir.1987)). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed functions, it anticipates." *Atlas Powder Co. v. 1RECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). Furthermore, one of skill in the art need not recognize the inherent subject matter prior to the date of invention[3]. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), *reh'g* and *reh'g en banc denied*.

[3] Lilly's Memorandum Regarding Inherent Anticipation and the Recognition Requirement is found at docket entry 286.

Prior art does not need to be published in a written document to constitute an invalidity defense under 35 U.S.C. § 102(b)[4]. Prior public use may also invalidate a patent by inherency and is defined as any use of the "invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134 (Fed. Cir. 1983). It is noteworthy that prior public use of the invention need not be extensive to serve as a bar to patentability. *National Research Dev. Corp. v. Varian Assocs*., 822 F. Supp. 1121, 1129 (D.N.J. 1993), *aff'd in part, vacated in part on other grounds*, 17 F.3d 1444 (Fed. Cir. 1994). And, like a prior publication there does not need to be a recognition of the inherent subject matter.

A. ESTROGEN

The earliest date of invention that Plaintiff's assert for the claimed methods for reducing NF-κB activity in cells is April 1989. Dr. Boyce testified that estrogen administered to post-menopausal women reduces NF-κB activity in cells. Thus, the administration of estrogen to post-menopausal women practices the claimed invention of the '516 patent.

Specifically, Dr. Boyce testified that estrogen regulates NF-κB activity in cells:

[4] Lilly's Memorandum Regarding The Statutory Bar to Patentability and the Public Use Doctrine is found at docket entry 303.

Q. Let's put up, if we could, PTX 1102. You remember testifying about this slide in your direct testimony, Dr. Boyce?
A. Yes.
Q. And this slide represents what happens in a post-menopausal woman?
A. Yes.
Q. And what's depicted here is that there is more osteoclast formation than osteoblast activity; is that fair?
A. Yes, overall.
Q. Overall. The balance is not right anymore?
A. Correct.
Q. And the reason the balance is not right is because a postmenopausal woman produces less estrogen?
A. As a consequence of the menopause, a number of things happen in a woman's body and reduction of estrogen is one of them.
Q. And reduction of estrogen contributes to more osteoclast formation?
A. It's associated with -- the increase in osteoclast formation is associated with a reduction in estrogen in women's blood.
Q. So just so I'm clear, so after menopause, a woman's estrogen goes down and osteoclast formation goes up; do I have that right?
A. As a consequence of menopause, estrogen and the levels of a number of other hormones go down, and osteoclast numbers go up.
Q. And osteoclast formation, increased osteoclast formation causes or requires NF-kappaB activity to go up?
A. Yes.
Q. So now we have three things linked in a woman after menopause: Estrogen goes down, osteoclast formation goes up, NF-kappaB activity goes up, correct?
A. Yes.

Trial Transcript, Day 4, 94:8-95:17.

Dr. Boyce further testified that estrogen was administered to post-menopausal women as Hormone Replacement Therapy ("HRT") as early as the 1940's, which is more than one year prior to the date of invention for the '516 patent. Specifically, Dr. Boyce testified as follows:

Q.	And if we administer estrogen to a woman after menopause, her estrogen level will go up, correct?
A.	It will go up if it's decreased, yes.
Q.	Well, after menopause it would be decreased, correct?
A.	Yes.
Q.	So if we give estrogen to a postmenopausal woman, her estrogen levels will go up, correct?
A.	Yes.
Q.	And her osteoclast formation will go down?
A.	Correct.
Q.	And her NF-kappaB activity will go down, correct?
A.	Correct.
Q.	And estrogen has been administered to women since the1940s, hasn't it, for, in part, preventing bone loss?
A.	The first discovery that estrogen reduces bone loss was made, I believe, in 1980, around 1980, I think.
Q.	Women have been receiving estrogen, postmenopausal women have been receiving estrogen since the 1940s, have they not, Dr. Boyce?
A.	I believe so.
Q.	And when those women received estrogen in the 1940s and the 1950s and the 1960s, their estrogen levels went up, correct?
A.	Yes.
Q.	Their osteoclast formation went down, correct?
A.	I presume so.
Q.	And their NF-kappaB activity went down, correct?

Trial Transcript, Day 4, 95:18-96:19.

This evidence is corroborated and supported by testimony from Lilly's expert Dr. Manolagas. Dr. Manolagas confirmed Dr. Boyce's testimony above (*Trial Transcript*, Day 8, 109:19-112:5), and elaborated further[5]:

[5] Additional supporting testimony on this issue may be found at *Trial Transcript*, Day 8, 109-123.

Q.	Can we please put the exhibit back up on the screen. Dr. Manolagas, the first line, 1942, that confirms your prior testimony that the Food and Drug Administration approved Premarin for treating menopausal symptoms and related conditions; is that correct?
A.	That is correct.
Q.	Premarin is a form of estrogen replacement therapy, correct?
A.	Correct.
Q.	Do you have an opinion as to whether Premarin as administered since 1942 for the, as estrogen replacement therapy, would reduce NF-kappaB activity as called for by the claims in the '516 patent?
A.	Correct. It will.

Trial Transcript, Day 8, 115:10-23.

Thus, both Dr. Boyce and Dr. Manolagas' testimony establishes by clear and convincing evidence that estrogen administered to post-menopausal women reduces NF-κB activity in cells. Both experts' testimony further establishes that estrogen was administered to post-menopausal women as early as the 1940's. Given that estrogen administered to post-menopausal women as HRT was in public use more than one year prior to the earliest filing date of the '516 patent, the claims of the '516 patent are anticipated.

B. RED WINE

Like estrogen, red wine was in public use well more than one year prior to the earliest filing date of the '516 patent. And, as Dr. Manolagas testified, red wine reduces NF-κB activity:

Q.	But what is your view, Dr. Manolagas, if any, as to whether compounds administered years before the patent in suit was even applied for and whether they reduce NF-kappaB activity?
A.	We just finished talking about estrogens. I have done experiments with the active form of vitamin D, which is another hormone. I know that corticosteroids, the drugs that are used for asthma, Crohn's disease, for rejection of transplantation, for rheumatoid arthritis, they've been used for many, many years, they decrease NF-kappaB. So there's a whole list of things that were used long before 1989 or '91. Aspirin decreases NF-kappaB. There are papers that talk about red wine decreasing NF-kappaB. And I guess in my part of the world red wine was used before '85.

Trial Transcript, Day 9, 49:21-50:9. (Emphasis added.)

C. CALCITRIOL

Similarly, calcitriol, a Vitamin D analog, anticipates the claimed invention. Dr. Manolagas provided testimony regarding cellular experiments published in peer reviewed journals showing clear inherent anticipation of the asserted claims[6]:

[6] Additional supporting testimony may be found at *Trial Transcript*, Day 9, 61-66.

> Q. Would you describe exactly what it is that you're trying to get across on this board?
>
> ….
>
> A. One, two, three, four, five, six studies done using human cells that includes monocytes and macrophages, stimulated with this chemical called phytohemagglutinin, PHA for short, and then treated with different concentrations of calcitriol. One that is common for all of these was 10 minus 8 molar. That was before '89 to '91.
>
> Then, after the inventors found NF-kappaB, I went back and said, is it possible that calcitriol affects NF-kappaB? And that's what we found in 1989 and 1991. So what that then establishes, that if you put human cells with PHA and calcitriol, you decrease NF-kappaB.
>
> The point I'm trying to argue here is that if that happens in, after 1991, in 1995, obviously it happened at that time, we did the same experiment. Remember the concept I told you with the pyramids? I had no idea then that there were a thing called NF-kappaB. Nobody knew until this inventor found it. But I did it then because I did it now.

Trial Transcript, Day 9, 63:23-64:18.

As Dr. Manolagas' testimony makes clear, NF-κB was inherently reduced in the calcitriol experiments performed prior to the effective filing date of the '516 patent and as such, the asserted claims of the '516 patent are anticipated by the prior publications cited by Dr. Manolagas during his testimony.

D. CYCLOSPORIN A

The evidence presented also proves that prior published experiments testing Cyclosporin A in cells necessarily inhibited NF-κB[7]. As Dr. Manolagas testified:

[7] Further evidence regarding inherent anticipation by Cyclosporin A may be found at *Trial Transcript*, Day 9, 66-75.

Q.	Would you just describe what that board represents?
A.	The same concept, the difference in time going twenty, hundred year, whatever you go. If before 1989, these guys took human cells – T stands for T lymphocytes -- they put the activator and they put the anti-rejection drug [cyclosporin A], and they did the same experiment later and found that NF-kappaB is inhibited, it's logical to say if it did it here, it did it then. It's the same experiment separated by ten, fifteen years. If it worked then, common sense says that it will have worked now, and vice versa, if it works now, it will have worked then.

Trial Transcript, Day 9, 70:18-71:3.

As Dr. Manolagas testified, prior public use of Cyclosporin A in patients also inherently anticipates the asserted claims of the '516 patent:

Q.	What relationship, using the board, if you would, does Holschermann have to these prior art references, Griffith, Griffith II and the 1985 Physicians Desk Reference?
A.	Well, if cyclosporin when given to patients suppressed NF-kappaB in 1997, whenever it was, certainly it would have done it before then, whether it was ten years or twenty years before or if we had a thousand years before, that's what it does, that's what it would have done then, nothing different. The concept is if it's true, it's going to be true across time and space.

Trial Transcript, Day 9, 72:22-73:3.

E. GLUCOCORTICOIDS

Lilly has presented ample evidence showing that dexamethazone inherently anticipated the claimed compounds in the prior art[8]. Dr. Manolagas testified that this steroid compound has been administered to patients for more than a year before the effective filing dates asserted for the '516 patent, and further that based on the teachings of one of the inventors of the '516 patent, this steroid inherently reduced NF-κB activity:

[8] Dr. Manolagas' testimony on this issue may be found at *Trial Transcript*, Day 9, 75-83.

Q. "In the presence of an activator such as TNF-alpha, newly released NF-kappaB reassociates with the dex-induced I-kappaB and thus reduces the amount of NF-kappaB translocating to the nucleus." Do you see that?
A. Yes.
Q. What exactly is Dr. Baldwin describing in this passage of the paper?
A. Inhibition of NF-kappaB by a synthetic glucocorticoid steroid called dexamethazone.
Q. Was dexamethazone administered to patients long before --
A. For a long, long time.
Q. More than a year before any of the effective filing dates asserted in this case?
A. Yes.

Trial Transcript, Day 9, 79:13-80:1.

F. SALICYLATES/ASPIRIN

Dr. Manolagas, in discussing prior art publications on the administration of salicylates to patients, provided extensive testimony proving that salicylates, and aspirin specifically, inherently anticipate the asserted claims of the '516 patent[9]. One of the inventors of the '516 patent himself advised the United States Patent and Trademark Office of this fact, as noted by Dr. Manolagas:

[9] Extensive testimonial evidence on this point may be found at *Trial Transcript*, Day 9, 83-93.

Q. If I could have you turn to, I believe it's Paragraph 9 of Defendant's Trial Exhibit 13. Would you describe -- and it bridges over to the second page, the next page, rather.
Would you describe what Dr. Baltimore said to the United States Patent Office with respect to whether or rather the mechanism of action of 5-ASA?
A. That it is one of the compounds that can inhibit NF-kappaB.
Q. So that treatment of cells with such compounds as, among other things, 5 aminosalicylic acid, that's 5-ASA; is that correct?
A. That's correct.
Q. Dr. Baltimore said in the '516 patent file history that it inhibits NF-kappaB-mediated gene expression, this 5-ASA compound, right?
A. He did.
Q. He cited, among other things, a Yan reference, Y-A-N. Do you see that?
A. Correct.
….
Q. That's a reference in the -- just leave that up for a second. That's --
A. Journal of Biological Chemistry again.
Q. What does the Yan reference show?
A. That this ASA inhibits NF-kappaB.
Q. And inhibits NF-kappaB, and as Dr. Baltimore put it, NF-kappaB-mediated gene expression; do you see that?
A. That's what they concluded.
Q. Well, based on Dr. Baltimore's representation, what conclusion, if any, can you draw about whether 5-ASA as administered since 1983 would necessarily have reduced NF-kappaB activity?
A. It would reduce NF-kappaB activity.

Trial Transcript, Day 9, 86:8-87:1, 87:11-20.

G. ANTIBIOTICS

Similarly, through the testimony of Dr. Manolagas, Lilly has shown that the prior public use administration of antibiotics inherently anticipate the asserted claims of the ‘516 patent:

Q.	Now, how long have antibiotics been administered for the treatment of gram-negative infections?
A.	I think from the time of Flemming, and that was just around the Second World War.
Q.	And as administered to patients for the treatment of gram-negative infections, what opinion do you have as to whether that would fall within the scope of these claims?
A.	If you decrease a product of a bacteria, which is LPS, by killing them, you will decrease NF-kappaB activity.
Q.	Now, will killing the cells immediately reduce LPS?
A.	Probably in the process of the killing you will release a little bit of LPS from the cells that are around there, but eventually if you kill the bacteria, there will be no LPS made by the bacteria.

Trial Transcript, Day 9, 95:3-16.

Thus, through prior public use administration, or prior publications, Lilly has clearly demonstrated that compounds such as estrogen, calcitriol, Cyclosporin A, glucocorticoids, antibiotics, and salisylates inherently anticipate the asserted claims of the '516 patent as these compounds necessarily reduced NF-κB activity more than one year prior to the asserted filing dates of the '516 patent.

IV. THE '516 PATENT IS INVALID UNDER 35 U.S.C. § 112, 1st Paragraph

A. THE CLAIMS ARE INVALID FOR LACK OF AN ENABLING DISCLOSURE

The asserted claims are so broad that they unlawfully encompass all possible steps for performing the specified function (reduction in NF-κB activity). The invalidity of a claim purporting to cover any and all means or steps for attaining a particular result is a matter of law. *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983).

Even brilliant scientists who have discovered a previously unappreciated natural phenomenon, and even those who have found one way to apply that phenomenon to a

useful end, have fallen prey to the temptation to try to patent any and all ways of employing that phenomenon to that end. *O'Reilly v. Morse*, 56 U.S, 62 (1854), illustrates the problem. Samuel B. Morse, the famed inventor of the telegraph, had discovered a way to use electromagnetism generated from an electric current to cause a telegraph instrument to print intelligible characters at a distance from the site where the message was sent. *Id*. at 112. The patent claims directed to the specific instrumentalities he developed to do so were upheld in every respect. *Id*. His eighth claim, however, directed to the use of an electric current, however developed, for printing intelligible characters at a distance, was st*ru*ck down. *Id*. at 113. As the Court observed:

> If this claim can be maintained, it matters not by what process or machinery the result is accomplished. For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification.
>
> ….
> In fine[,] he claims a*n* exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent. The court is of opinion that the claim is too broad, and not warranted by law.

Id. This is precisely the defect in the asserted claims of the '516 patent. The defect in Morse's eighth claim was that it was much broader in scope than the enabling disclosure he provided in his patent specification. The defect is now recognized as a failure to provide an enabling disclosure commensurate in scope with the claim in violation of 35 U.S.C. § 112, first paragraph. *See In re Hyatt* at 714. In the special case where a claim purports to cover any and all means or steps for attaining a particular result, the invalidity of the claim follows as a matter of law. *Id*. It is impossible to present an adequate

enabling disclosure of every conceivable way of achieving a particular result. *Id*. As this Court aptly noted at the beginning of the Markman hearing in this case, "[e]ach of these claims talks about a method, and each of the claims describes a method for doing something, but it doesn't say what the method is. It simply gives the end result." (Markman Tr. 4:3-6 (Ex. J).)

B. THE CLAIMS ARE INVALID FOR LACK OF AN ADEQUATE WRITTEN DESCRIPTION

Defining materials essential to the practice of an invention simply by what they do or by how they might be discovered rather than by reference to their structure or other identifying characteristics is legally insufficient. Such functional descriptions are but "a mere wish or plan for obtaining the claimed chemical invention." *UC v. Lilly*, 119 F.3d 1559, 1566 (Fed. Cir. 1997); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993); *Rochester*, 358 F.3d 916, 927 (Fed. Cir. 2004). A written description sufficient to support a claim to use of a large genus of materials requires either a description of a sufficient number of representative species falling within the genus or the description of common structural features possessed by members of the genus. *Enzo Biochem, Inc. v. Gen-Probe Inc*., 323 F.3d 956, 967 (Fed. Cir. 2002); UC v. Lilly, 119 F.3d at 1569. Functional characteristics may serve to describe the compounds only if coupled with a known or disclosed correlation between structure and function. Enzo, 323 F.3d at 964. Identification of a single species has been repeatedly held to be insufficient to constitute a description of a broad generic invention in the biological sciences because of the inherent unpredictability of performance in complex biological systems. See *UC v. Lilly*, 119 F.3d at 1569; *Noelle v.Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004).

1. The ‘516 Patent Doesn’t Describe Any Useable Drugs

The claims of the ‘516 patent are directed to, at minimum, methods for reducing NF-κB activity. This method necessarily mandates an NF-κB inhibitor, therefore the specification would need to disclose, at bare minimum, one such inhibitor in order to support the claimed invention. It does no such thing.

As Dr. Latchman testified, the ‘516 patent discusses blocking NF-κB with IkB, but fails to disclose the sequence of IkB or a method to introduce it into a cell:

Q.	What disclosure is there in the '516 patent of I-kappaB actually being introduced as an inhibitor of NF-kappaB activity in cells?
A.	There is no disclosure…

Trial Transcript, Day 11, 124:1-4.

Q.	Well, would you tell the jury what the error in Figure 43 means with respect to what opinion, if any, you have as to whether the inventors were in possession of the claimed invention as of November 1991.
A.	Well, clearly, insofar as what is in the '516 patent, which is in my understanding a written description, there is no sequence there of human or mammalian I-kappaB DNA.

Trial Transcript, Day 11, 140:10-16.

Dr. Latchman’s testimony was essentially the same with regard to the suggestion within the ‘516 patent that decoy molecules could be used to inhibit NF-κB activity:

Q.	Well, another issue that was raised by Dr. Maniatis was the decoy molecules. This is PTX 1045. He has asserted that these were disclosed in the '516 patent. Do you agree?
A.	I agree that the possibility of using decoy molecules is certainly mentioned in the '516 patent.
Q.	Were any actual decoy molecules described in the '516 patent, Dr. Latchman?
A.	Not in the way that would allow one to use them.

Trial Transcript, Day 11, 140:17-24.

Dr. Latchman's testimony makes clear that the same principles apply to the disclosure of the '516 patent regarding dominating interfering molecules:

> Q. And to use decoy molecules or dominantly interfering molecules in human therapy would involve the formidable obstacles and practical and open and serious questions that Dr. Baltimore or the inventors referred to in his critique?
> A. Certainly, at the time of the patent, 1989-1991, yes.
> Q. To what extent, if at all, Dr. Latchman, is there enough information in the '516 patent to make I-kappaB decoy molecules or dominantly interfering molecules to reduce NF-kappaB activity in cells?
> A. I don't think there is sufficient information to make such molecules.
> Q. Even if you could make them, to what extent is there enough information in the '516 patent to use them in human therapy?
> A. I think there is not, information is not given as to how you could use such molecules in human therapy.

Trial Transcript, Day 11, 152:16-153:7.

Finally, as noted by Dr. Latchman, the '516 patent discloses no small molecules:

> Q. What small-molecule compounds, Dr. Latchman, are actually disclosed in the '516 patent as inhibitors of NF-kappaB activity?
> A. There is no disclosure of the formula structure of any small molecule which could inhibit NF-kappaB activity in the patent.
> Q. Well, is any small molecule that could be an inhibitor of NF-kappaB even referenced by name anywhere in the '516 patent?
> A. No.
> Q. What is your view as to whether small molecule compounds are described, whether by structure or some other way in the '516 patent?
> A. There is no description of the structure of such small organic molecules.
> Q. Any characteristics or anything?
> A. No.

Trial Transcript, Day 11, 153:1-154:15

V. LILLY DOES *NOT* INFRINGE THE '516 PATENT

Lilly renews its earlier filed JMOL directed to non-infringement because 1) Plaintiffs have failed to introduce any evidence sufficient to prove infringement and 2) as a matter of law this Court should enter a judgment of non-infringement.

A. NO PROOF OF DIRECT INFRINGEMENT

The claims of the '516 patent are method claims, specifically methods requiring the step of reducing NF-κB activity in cells. For there to be a finding of ***direct*** infringement there must be evidence that someone performs each step of the claimed methods. The only two possible "someones" are Lilly itself and the patients that actually take Lilly's Evista® and Xigris® products.

1. Lilly Does Not (And Cannot) Directly Infringe the '516 Patent

Corporations, like Lilly, have no NF-κB activity to reduce. As such, even Plaintiffs had to concede that they do not intend to introduce evidence of direct infringement by Lilly. *Pl. Resp. Def. Motion in Limine to Exclude Evidence of Direct Infringment; Doc. No. 257*. And, in fact, Plaintiffs did not introduce any such evidence in their case-in-chief. Thus, in view of Plaintiffs' concession and their failure to introduce evidence, JMOL is appropriate on the issue of direct infringement by Lilly.

B. NO PROOF OF INDIRECT INFRINGEMENT

A prerequisite to a finding of either induced or contributory infringement is the necessary act of direct infringement; absent direct infringement there can be ***no*** indirect infringement. *See, e.g., Deepsouth Packing Co. v. Laitram Corp.,* 406 U.S. 518 (1972).

As discussed above, Plaintiffs have failed to introduce any evidence on direct infringement by Lilly. Likewise, they failed to show that any patient directly infringes when taking the accused drugs for the indications stated in the FDA label.[10] Therefore, JMOL is appropriate on the issue of indirect infringement as well.

1. Patients Taking Evista® and Xigris®
Do ***Not*** Directly Infringe the '516 Patent

The first requirement for both contributory and induced infringement is direct infringement by ***someone***. *See Dynacore Holdings Corp. v. U.S. Philips Corp.,* 363 F.3d 1263 (Fed. Cir. 2004) (affirming summary judgment of no induced or contributory infringement)***;*** *Jansen v. Rexall Sundown, Inc.,* 342 F.3d 1329, 1334 (Fed. Cir. 2003) (affirming grant of summary judgment of no induced or contributory infringement). Plaintiffs have failed to introduce any evidence whatsoever to support a claim of direct infringement by patients who take Evista® or Xigris ® according to the product label. Without knowing her NF-κB level of activity before and after taking Evista® or Xigris ® (through either direct or indirect evidence) there can be no evidence that the patient's NF-κB activity was induced prior to taking Evista® or Xigris ® or that it was reduced afterward.

Plaintiffs' only evidence related to patients was introduced by the deposition testimony of Ms. Dain Waters and Dr. Stanley Nasraway, but their testimony failed to provide any evidence of direct infringement.[11] Even Plaintiffs' own technical expert, Dr.

[10] Plaintiffs have stated unequivocally that the alleged infringement is that when patients take Evista or Xigris in accordance with the prescribed label, they practice the claimed methods. *Plaintiffs' Trial Brief*, pg. 2.

[11] In order to establish infringement of the claims in suit, Plaintiff must show that the alleged infringers perform each and every step of the claimed method. At minimum, in order for Plaintiffs to prevail the evidence must show that there is a reduction in induced NF-κB activity. (The asserted claims each require

Boyce, admitted that not all patients taking Evista® (according to the product label or off label) will necessarily infringe.

2. Plaintiffs Have ***Failed*** to Prove Contributory Infringement

Direct infringement must be shown before there can be a finding of indirect infringement. As stated above, Plaintiffs failed to prove direct infringement by 1) Lilly itself and 2) by patients. Even assuming *arguendo* that direct infringement exists, Plaintiffs further failed to meet the other requirements for proving indirect infringement.

To prove contributory infringement, as outlined in the statute itself, Plaintiffs must establish that the use of Evista® and Xigris® are 1) a material part of the claimed methods, 2) Lilly sold Evista® and Xigris® knowing that they were especially made or adapted for use in the claimed methods and 3) Evista® and Xigris® are not staple articles of commerce suitable for any substantial noninfringing use. Plaintiffs have failed to introduce evidence on any of these elements and in fact testimony supports that these three elements cannot be proven. At the outset, both of Lilly's products were in fact launched prior to the issuance of the '516 patent claims, thus there is no way that Lilly could have known that the products manufactured and sold "were especially made or adapted for use in the claimed methods"

With regard to the first element, there has been no evidence introduced that Lilly's two drugs are "a material part" of any of the claims of the '516 patent. A review of the four claims being asserted by Plaintiffs clearly shows that the active ingredients in Lilly's drugs are not mentioned anywhere. Indeed, no specific chemical compounds

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reducing induced NF-κB activity, and a consequent reduction of specific NF-κB mediated effects (*i.e.* claim 80 recites that NF-κB mediated effects of external influences that induce NF-κB-mediated signaling are modified; claim 95 recites that expression of genes activated by extracellular influences that induce NF-κB intracellular signaling is reduced; and claims 144 and 145 recite that LPS-induced expression of cytokines is reduced).

(certainly not raloxifene or activated Protein C, the active ingredients in Evista® and Xigris®, respectively) are taught anywhere in the '516 patent for use in connection with the method of reducing NF-κB activity. Furthermore, the specific diseases for which Lilly's two drugs are prescribed (i.e. postmenopausal osteoporosis (Evista®) and severe sepsis (Xigris®) are nowhere mentioned in either the specification or claims of the '516 patent.

Recognition by Plaintiffs' own witness that Lilly did not market Evista® as made or adapted for reduction of NF-κB activity, *i.e.* for use in the claimed methods, clearly shows that Plaintiffs have failed to produce evidence supporting contributory infringement. Likewise, with regard to Xigris®, Plaintiffs' other technical expert, Dr. Livingston testified that he could ***not*** confirm if more than 20% of patients taking Xigris® would have their NF-κB activity lowered. The use of Xigris® among these patients who do not have detectable LPS, and therefore cannot have LPS-induced expression of cytokines, demonstrates that Xigris®, like Evista®, is a staple article of commerce having substantial non-infringing uses. As such, Lilly cannot be held liable as a contributory infringer.

3. Plaintiffs Have ***Not*** Proved Inducement of Infringement

Plaintiffs also failed to show that Lilly had the requisite intent to actively induce patients to directly infringe. To establish inducement of infringement Plaintiffs must establish that Lilly knowingly induced infringement, and that Lilly had the specific ***intent*** to encourage another's infringement. *MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005) (quoting *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304-05 (Fed. Cir. 2002)).

"The mere sale of a product capable of substantial noninfringing uses does not constitute indirect infringement of a patent." *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1274 (Fed. Cir. 2004). Thus, to prove inducement, Plaintiffs here must prove either (1) that in ***all*** instances patients complying with the product label would necessarily infringe the asserted claims of the '516 patent, or (2) that Lilly specifically instructed or encouraged a particular patient or a particular group of patients to take the product in such a manner that would directly infringe. *Id*. at 1275-1276.

Plaintiffs have failed to introduce evidence supporting either option. Indeed, Plaintiffs have failed to provide any evidence that in ***all*** instances patients complying with the product label would necessarily infringe the asserted claims of the '516 patent, *i.e.* ***all*** patients would experience a reduction in NF-κB levels. Similarly, Plaintiffs have failed to provide evidence that Lilly specifically instructed or encouraged a particular patient or a particular group of patients to take the accused products in such a manner that would directly infringe

Plaintiffs' experts have admitted that not all patients treated with Evista® or Xigris® would necessarily infringe. Thus, those patients taking the products who do not infringe constitute a substantial noninfringing use, and Plaintiffs must show that Lilly did something to promote the products specifically to that group of patients who would be direct infringers. The legal basis for judgment as a matter of law in this case is identical to the *Dynacore* case, in which the Federal Circuit affirmed summary judgment of no induced or contributory infringement absent specific instances of direct infringement. Similarly, in the *Jansen* case, the Federal Circuit affirmed summary judgment of no indirect infringement (no inducement or contributory infringement) where the there was

little evidence of direct infringement by customers and the plaintiff could not show that use according to the label would necessarily infringe.[12] Simply put, under both the *Dynacore* and *Jansen* case, it is not sufficient for inducement to simply sell a product with instructions for use where patients following those instructions will not necessarily infringe. "Sometimes it will, and sometimes it won't" is not enough.

VI. PLAINTIFFS *FAILED* TO PROVE DAMAGES

. Lilly also renews its request for a judgment of no damages because Plaintiffs have failed to introduce any evidence that specific patients have directly infringed the claimed methods. In fact, Plaintiffs own experts have testified that they do not know whether more than 50% of Evista® and 20% of Xigris® patients actually have their NF-κB activity lowered.

Plaintiffs have failed to introduce any evidence that specific patients have directly infringed the claimed methods. In fact, as indicated above, Plaintiffs own experts, Drs. Boyce and Livingston, have testified that they do not know whether more than 50% of Evista® and more than 20% Xigris® patients actually have there NF-κB lowered. Any damages awarded must be calculated using a royalty base that reflects sales related to direct infringement. The evidence shows that at least 50% of Evista® sales and at least 80% of Xigris® sales likely as not do not reduce NF-κB activity in patients. As such,

[12] In *Jansen*, the claims covered a method for treating or preventing a type of anemia by administering a specific oral dose to a person "in need thereof." The product sold by the defendant was an over-the-counter vitamin complex having other potential uses; as such there was no contributory infringement as a matter of law. Furthermore, the instructions for use did not suggest that persons take the vitamin complex only if they needed to prevent or treat anemia and were therefore "in need []of" the medication for that disease. Thus, the Court found as a matter of law that the Plaintiff failed to prove inducement.

Likewise, in this case, Plaintiffs' experts have admitted that a substantial percentage of patients treated with Evista® or Xigris® will not infringe (no contributory infringement) and that Lilly does not specifically promote the sale of either of these products for any particular use that will infringe (no inducement).

Plaintiffs could not specifically quantify a specific royalty base for which to calculate total damages and thus did not sustain their burden of proof.

As noted above, the *Dynacore* case makes clear that – absent proof that these compounds when administered to patients necessarily infringe (and Plaintiffs' experts have admitted they do not) – Plaintiffs must "point to a specific instance of direct infringement and restrict its suit to liability stemming from that specific instance." *Dynacore,* 363 F.3d at 1275-6. Plaintiffs' experts did not opine that any patient's NF-κB activity was reduced, or that the NF-κB activity was reduced in any Xigris® patients. Plaintiffs' experts also did not opine that any NF-κB mediated gene expression was in fact reduced in patients.

As such, Plaintiffs have failed to prove even a single specific instance of direct infringement. Its suit for liability must therefore be restricted to "zero." Lilly requests, therefore, that the Court enter a judgment as a matter of law that Lilly owes no damages to Plaintiffs.

VII. CONCLUSION

For the reasons set fort above, Lilly requests that the Court enter as a matter of law a judgment finding that Lilly has not infringed any of the four asserted claims of the '516 patent, that the '516 patent is invalid, and that Lilly owes no damages to Plaintiffs because there is no evidence of direct (or indirect) infringement by patients.

Respectfully submitted,

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